REMARKS

Claim 15 has been cancelled. Claims 1, 13, 14 and 16 have been amended. New claim 17 is added. Claims 1-14 and 16-17 are now pending in this application. Support for the amendments is found in the existing claims and the specification as discussed below.

Basis for the amendment of claim 1 is present in the application as filed in the present specification page 18, lines 16-18; page 19, line 31 to page 20, last line; page 25, lines 7-13; Figures 28-35 and Example 8 (page 46, line 20 to page 50, line 4) corresponding to the published application at paragraphs [0139]; [0144] to [0148]; [0178]; and [286] to [312].

Basis for the amendment to claim 14 is found in the present specification at page 48, lines 14-17 which corresponds to paragraph [0300] of the published application.

Basis for the amendment of claim 16 is present in the application as filed at page 6, lines 10-11; page 12, line 28 to page 13, line 5; page 28, lines 7-10; and lines 24-25 corresponding to the published application at paragraphs [0048], [0109], [0196], and [0199].

New claim 17 was added. Basis for claim 17 is present in the application as filed on page 6, lines 13-20 corresponding to the published application at paragraph [0049].

Accordingly, the amendments do not constitute the addition of new matter. Applicant respectfully requests the entry of the amendments and reconsideration of the application in view of the amendments and the following remarks.

Election of species requirement

Applicants confirm the election of calotropin and 2" oxo-voruscharin as the active compounds, the election of lung cancer as the cancer and the election of vincristine as the therapeutic compound.

It is not clear why claims 6 and 7 are withdrawn as claim 7 recites "vincristine", which is an elected compound and depends from claim 6. Reconsideration of the withdrawal of claims 6 and 7 is respectfully requested.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 1-7, 11, 12, and 16 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention.

The Office Action states that claim 1 is indefinite because what are considered "relevant detrimental side effects" is unclear.

With this amendment, claim 1 has been amended to clarify that the detrimental side effects relate to "reducing toxic side effects caused by a therapeutic compound and/or a physical radiation on normal, non-cancer related cells, tissues or organs".

In view of Applicants' amendments, reconsideration and withdrawal of the above ground of rejection is requested.

Rejection under 35 U.S.C. § 102(b) (Mrak)

Claim 16 is rejected under 35 U.S.C. § 102 (b) as anticipated by Mrak (CH 679012 A).

Amended claim 16 clearly indicates that the kit comprises "an extract of *Calotropis procera* as defined in claim 1 in a first container, and an anti-cancer agent that exerts toxic side effects on normal, non-cancer related cells, tissues or organs in a second container". Moreover, the anti-cancer agent is defined as an agent that exerts toxic side effects on normal, non-cancer related cells, tissues or organs. Amended claim 17 provides a list of anti-cancer agents.

Applicants stress that there is an apparent difference between the "extract" and the "anti-cancer agent". Upon reading the specification of the patent application it is clear that the anti-cancer agent is not considered to include a plant extract, but that the anti-cancer agent is a pharmaceutical agent that is used to treat cancer and that shows side effects on normal cells. Moreover, the plant extracts disclosed in Mrak are cited to be useful for the treatment of syphilis, and not for treating cancer. There is no indication in Mrak that the cited extracts have anti-cancer activity and/or that they exert toxic side effects on normal, non-cancer related cells, tissues or organs. The extracts of Mrak should therefore not be considered to represent "anti-cancer agents". Accordingly, Mrak does not teach all of the components of the kit as claimed.

In view of Applicants' amendments and arguments, reconsideration and withdrawal of the above ground of rejection is respectfully requested.

Rejections under 35 U.S.C. § 102(b)/103(a) (Hussein)

Claim 14 is rejected under 35 U.S.C. § 102 (b) as anticipated by, or in the alternative, under 35 U.S.C. § 103(a) as obvious over Hussein, et al. (Journal of Chemical Ecology (1994), vol. 20, no. 1, pp. 135-140).

Applicants submit that the present extract, as claimed in claim 14 and obtained with the method of claim 13, is different from the extracts obtained with the method of Hussein et al. Claim 14 has been amended to recite that the active extract is "capable of reducing the toxic effects of an anti-tumor compound". Applicants submit that by applying the present extraction method, the present extract obtains the claimed characteristics that are absent in the prior art extracts of Hussein. In particular, by applying the present extraction method, the extract receives an anti-poisonous property and is able to reduce the toxic effects of an anti-tumor compound. This is clearly exemplified in the present invention, e.g., in example 8 and in figures 28 to 35. Hussein, et al. do not report this kind of property for the extracts prepared.

Furthermore, the extract of Hussein, et al. is different from the extract taught by Applicants. Hussein, et al. teach extraction of the latex or milky sap of *C. procera* using ethanol (see page 136, lines 1-6 under "Methods and Materials"). In contrast, Applicants' Example 1 teaches extraction of *C. procera* roots (see Example 1, especially page 30, line 19) as a preferred embodiment.

The latex of *Calotropis* is distinct from the fruits, aerial parts and subterranean parts as claimed. While the aerial parts may contain some latex, if one of ordinary skill in the art were interested in an extract of the plant sap, then one of ordinary skill in the art would logically start by isolating the plant sap as taught by Hussein, et al. and not with a fruit, a subterranean part or even an aerial part as taught by Applicants.

In order to more clearly distinguish the claimed invention from Hussein, et al., the term "aerial parts" has been deleted from claim 13. The product obtained by Hussein, et al. is clearly different from Applicants' claimed product in view of the different starting material

In view of the different starting material and different properties of the extract obtained, Applicants respectfully submit that the extract of claim 14 is patentable over Hussein, et al.

In view of Applicants' amendments and arguments, reconsideration and withdrawal of the rejection based upon Hussein, et al. is respectfully requested.

Rejections under 35 U.S.C. § 102(b)/103(a) (Alkofahi)

Claim 14 is rejected under 35 U.S.C. § 102 (b) as anticipated by, or in the alternative, under 35 U.S.C. § 103(a) as obvious over Alkofahi, et al. (Int. J. Crude Drug Res. (1990), vol. 28, no. 2, pp 139-144).

Applicants submit that the present extract, as claimed in claim 14 and obtained with the method of claim 13, is different from the extracts obtained with the method of Alkofahi, et al. Claim 14 has been amended to recite that the active extract is "capable of reducing the toxic effects of an anti-tumor compound". Applicants submit that by applying the present extraction method, the present extract obtains the claimed characteristics that are absent in the prior art extracts of Alkofahi, et al. In particular, by applying the present extraction method, the extract receives an anti-poisonous property and is able to reduce the toxic effects of an anti-tumor compound. This is clearly exemplified in the present invention, e.g., in example 8 and in figures 28 to 35 of the present specification. Alkofahi, et al. do not report this kind of property for the extracts prepared. Accordingly, Alkofahi, et al. do not teach the claimed extract.

In view of Applicants' amendments and arguments, reconsideration and withdrawal of the above ground of rejection is respectfully requested.

Rejections under 35 U.S.C. § 102(b)/103(a) (Stimson)

Claim 14 is rejected under 35 U.S.C. § 102 (b) as anticipated by, or in the alternative, under 35 U.S.C. § 103(a) as obvious over Stimson (WO 98/52562).

Applicants submit that the present extract, as claimed in claim 14 and obtained with the method of claim 13, is different from the extracts obtained with the method of Stimson. Claim 14 has been amended to recite that the active extract is "capable of reducing the toxic effects of an anti-tumor compound". Applicants submit that by applying the present extraction method, the present extract obtains the claimed characteristics that are absent in the prior art extracts of Stimson. In particular, by applying the present extraction method the extract receives an anti-poisonous property and is able to reduce the toxic effects of an anti-tumor compound. This is clearly exemplified in the present invention, e.g., in the present specification, example 8 and in figures 28 to 35. Stimson does not report this kind of property for the extracts prepared.

Furthermore, the extract of Stimson differs from Applicants' claimed extract in several respects. Stimson begins extraction using a different *Calotropis gigantea* species than the *C. procera* of Applicants' claims. Accordingly, the starting material is different. Stimson teaches extraction first with petroleum ether (60-80), then ethyl acetate and finally methanol. However, it is the ethyl acetate fraction, not the methanolic fraction, that contains the cytotoxic activity (see Stimson, page 7, lines 13-14; page 7, lines 26-28; page 7, line 34 to page 8, line 8; page 8, lines

26-30). Accordingly, as the fraction characterized by Stimson is different from the fraction of Applicants' method claim 13, the product of claim 14 obtained by the method steps of claim 13 is clearly different from the product taught by Stimson.

Furthermore, Stimson teaches away from any characterization of a methanolic fraction in teaching that the cytotoxic activity resides in the ethyl acetate fractions. Accordingly, Stimson teaches a different method not taught by the present inventors and obtains an ethyl acetate, not a methanolic fraction. Stimson does not teach the claimed characteristics of Applicants' claimed extract which is the reduction of the toxic effects of an anti-tumor compound. Clearly, the product of Stimson is different from Applicants' claimed product.

In view of Applicants' amendments and arguments, reconsideration and withdrawal of the above ground of rejection is respectfully requested.

Rejections under 35 U.S.C. § 103(a)

Claims 1-7, 11, 12 and 16 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Alkofahi, et al. (Int. J. Crude Drug Res. (1990), vol. 28, no. 2, pp. 139-144) in view of Sunkara (US Patent No. 4,904,697).

Claims 1-7, 11, 12, and 16 are rejected under 35 U.S.C. § 103 (a) as being unpatentable over Stimson (WO 98/52562) in view of Sunkara (US Patent No. 4,904,697).

These two grounds of rejection will be addressed together. Alkofahi, et al. and Stimson have been addressed above and these comments are incorporated here by reference.

In response to these two grounds of rejection, claim 1 has been amended to more clearly present the nonobvious features of the invention.

Amended claim 1 is directed to a *method of reducing toxic side effects* caused by a therapeutic compound and/or a physical radiation on normal, non cancer related cells, tissues or organs. The method comprises the sequential or simultaneous administration of the therapeutic compound and/or the physical radiation with an extract of a *Calotropis procera* plant "whereby said toxic side effects are reduced".

The *Calotropis* extract of the invention is not used as an anti-cancer agent for treating cancer by means of combination therapy, as suggested in the Office Action. In contrast, the *Calotropis* extract of invention is used as an "anti-dote". Applicants point out that Alkofahi,

Sunkara and Stimson do not teach that the side effects of known anti-cancer compounds can be reduced when combining the anti-cancer therapies with the administration of an extract of *Calotropis*.

A difference between the present invention and the cited prior art (Alkofahi, Sunkara, Stimson) is that the present invention provides for the combined administration of a *Calotropis* extract with a therapeutic compound and/or a physical radiation. None of Alkofahi, Sunkara and Stimson teach a combination of an extract from *Calotropis procera* with therapeutic compounds and/or physical radiation. Accordingly, the cited references, taken separately or together, do not teach all of the elements of the claimed invention.

Combination administration as claimed leads to a reduction in the toxic side effects caused by the therapeutic compound and/or the physical radiation. This is exemplified in the present application, for instance, in example 8. Example 8 teaches administration of a mortal dose of the anti-cancer agent vincristine (see present specification, page 48, lines 14-17). Co-administration of a *C. procera* extract counteracts the effects of the mortal dose of the anti-cancer drug.

Neither Alkofahi nor Stimson teach the use of an extract of *C. procera* in combination with other drugs. The Examiner cites Sunkara for teaching combination therapy, using more than one anti-cancer treatment together and that "It is well known that it is prima facie obvious to combine two or more ingredients each of which is taught by the prior art to be useful for the same purpose in order to form a third composition which is useful for the same purpose" (Office Action, page 7, last paragraph). However, in the present case, addition of a second "anti-cancer" drug would only serve to kill the test animals more quickly because adriamycine and vincristine are already administered at a mortal dose (See present specification, Figure 29 and page 48, lines 10-12, for example). A novel and unexpected aspect of Applicants' claimed invention is that co-administration of an extract of *Calotropis procera* is effective to reverse the toxic effects of anti-cancer drugs. By combined administration of a therapeutic compound and/or a physical radiation and the *Calotropis procera* extract of the claimed invention, more than just an additive effect is obtained. Rather, a synergistic effect is obtained since the therapy is improved *AND* an alleviation of side-effects caused by the administered anti-cancer compounds is obtained.

There is no teaching in any of Alkofahi, Sunkara or Stimson that toxic side effects of a therapeutic compound and/or a physical radiation can be reduced by the administration of a *Calotropis* extract in combination with such therapeutic compound and/or physical radiation. In contrast, a skilled person wanting to reduce toxic side effects of anti-cancer agents would definitely not be prompted to combine several compounds known to have anti-cancer activity. One of ordinary skill in the art would expect that the more anti-cancer compounds are combined, the greater the anti-cancer effect becomes, but also the greater the induced side effects. However, surprisingly, the present invention shows that this is not the case. Better anti-cancer effects can be obtained without increased toxicity towards healthy cells by a combined administration of a therapeutic compound and/or a physical radiation and the *Calotropis* extract of the invention.

Accordingly, Applicants respectfully submit that the nonobvious characteristic of the present method, as claimed in claim 1, resides in the use of an extract of *Calotropis procera* as an anti-dote, and thus resides in the combination of such extract with anti-cancer agents to decrease the toxicity (the toxic side effects) of these anti-cancer agents.

In view of the above, the Applicant respectfully submits that the subject of claim 1 is to be considered as nonobvious, in view of Alkofahi, Sunkara or Stimson, either taken alone or in combination.

Claim 13 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Hussein, et al. (Journal of Chemical Ecology (1994) vol. 20, no. 1).

Hussein, et al. teach extraction of the latex or milky sap of *C. procera* using ethanol (see page 136, lines 1-6 under "Methods and Materials"). In contrast, Applicants' Example 1 teaches extraction of *C. procera* roots (see Example 1, particularly page 30, line 19) as a preferred embodiment.

The latex of *Calotropis* is distinct from the fruits, aerial parts and subterranean parts as claimed. While the aerial parts may contain some latex, if one of ordinary skill in the art were interested in an extract of the plant sap, then one of ordinary skill in the art would logically start by isolating the plant sap as taught by Hussein, et al. and not with an aerial part as taught by Applicants.

In order to more clearly distinguish the claimed invention from Hussein, et al., the term "aerial parts" has been deleted from claim 13. The product obtained by Hussein, et al. is clearly different from Applicants' claimed product in view of the different starting material.

In view of Applicants' amendments and arguments, reconsideration and withdrawal of the above ground of rejection is respectfully requested.

CONCLUSION

In view of Applicants' amendments to the claims and the foregoing Remarks, it is respectfully submitted that the present application is in condition for allowance. Should the Examiner have any remaining concerns which might prevent the prompt allowance of the application, the Examiner is respectfully invited to contact the undersigned at the telephone number appearing below.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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Dated: July 19, 2007

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